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Stability of Extemporaneously Prepared Lansoprazole Suspension at Two Temperatures

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Stability of Extemporaneously Prepared Lansoprazole Suspension at Two Temperatures

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OBJECTIVE The purpose of this study was to examine the stability of a generic lansoprazole product in a 3 mg/mL sodium bicarbonate suspension under room temperature and refrigerated conditions.

METHODS Lansoprazole suspensions (3 mg/mL) were prepared in triplicate using an 8.4% sodium bicarbonate vehicle for each storage condition (room temperature and refrigerated). During 1 month, samples from each replicate were periodically removed and analyzed for lansoprazole concentration by liquid chromatography–tandem mass spectrometry (LC-MS/MS). Each sample was spiked with 10 mg/L omeprazole to serve as the internal standard. A positive electrospray LC-MS/MS method was validated over the calibration range of 5 to 25 mg/L using Food and Drug Administration Guidance. The identities of the analyte and internal standard in the samples were verified by monitoring the MS/MS transitions of m/z 370 to m/z 252 and m/z 346 to m/z 198 for lansoprazole and omeprazole, respectively. Additionally, the pH of the suspensions was monitored throughout the study.

RESULTS The stability of lansoprazole in the oral sodium bicarbonate suspension under refrigeration is compromised prior to what has been previously reported in the literature. Samples kept at room temperature lost >10% of the lansoprazole after 48 hours compared with the refrigerated samples, which maintained integrity up to 7 days. No statistically significant difference was found between the pH of the room temperature and refrigerated suspension samples, indicating that this factor is not the cause for the differences in stability at these two conditions.

CONCLUSIONS This study suggests that the extemporaneously compounded lansoprazole oral suspension prepared in 8.4% sodium bicarbonate should not be stored in plastic oral syringes longer than 48 hours at room temperature and no longer than 7 days when refrigerated. These data indicate an expiration time earlier than that previously reported for the refrigerated product (14 days).

INDEX TERMS drug stability, lansoprazole, suspensions

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INTRODUCTION

Proton pump inhibitors (PPIs) are medications that decrease the amount of acid produced by gastric parietal cells via the inhibition of the H⁺/K⁺ ATPase enzyme system. Uses for this class include gastroesophageal reflux disease, prevention of stress-induced ulcers, and treatment of Barrett esophagus, in adults. Lansoprazole has an indication for treating pediatric patients (ages 1–11 years) but lacks established safety or effectiveness data for children younger than 1 year. Even without the data for use in the neonatal population, PPI use has become routine. The North American Society for Pediatric Gastroenterology, Hepatol-

ogy and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommend the use of PPIs in neonates (>3 days and without complications) for the treatment of gastroesophageal reflux.¹

Aside from the dearth of safety and effectiveness information, another obstacle in using PPIs in neonatal and pediatric patients is the vehicle of administration. Commonly, adults using PPIs will receive the medication in a capsule form, but this is not always practical for younger patients. Suspensions are often used in these populations for PPI administration. In a prospective study performed by Lugo et al,² that included 21 children's hospitals, an oral suspension of lansopra-

zole was the number one reported extemporaneous formulation prepared in the inpatient setting. In the study, 19 of 21 hospitals surveyed reported using a 3 mg/mL lansoprazole oral suspension; however, there are limited data regarding the stability of this formulation.²

Olabisi et al³ examined preparations of lansoprazole for nasogastric tube administration. The study included lansoprazole mixed with a variety of vehicles, including apple juice, cranberry juice, ginger ale, orange juice, water, and sodium bicarbonate 8.4%. The suspensions were then passed through a nasogastric (NG) tube and collected in a graduated cylinder. Of all of the tested vehicles, sodium bicarbonate 8.4% was the only one found to provide complete drug retrieval after administration through the NG tube. Lansoprazole mixed with sodium bicarbonate 8.4% was also the only tested combination that did not result in any clogging in the NG tube, but despite this, the manufacturer still recommends the use of apple juice for NG tube administration of Prevacid.^{3,4} An alternative formulation of lansoprazole in Ora-Blend has been recently proposed by Melkoumov et al,⁵ yet the stability is limited to 3 days under refrigeration.

Preparing lansoprazole suspension in the 8.4% sodium bicarbonate vehicle, known as simplified lansoprazole suspension (SLS), is the historical standard⁶; however, studies examining the stability of the drug in this basic suspension are conflicting. According to a study by DiGiacinto et al,⁷ the reported stability of lansoprazole suspension was 8 hours at 22°C and 14 days at 4°C. In contrast, a study performed by Phillips et al⁸ revealed a stability of 4 weeks when lansoprazole was stored in amber plastic vials under refrigeration and 2 weeks at room temperature. Thus, the commonly accepted stability of lansoprazole suspension prepared in 8.4% sodium bicarbonate is 14 days if kept refrigerated.⁹ The objective of this study was to verify the stability (NLT 90% and NTM 110% of the labeled amount)¹⁰ of a lansoprazole suspension at both room and refrigerated temperatures.

MATERIALS AND METHODS

Instrumentation and Calibration

Previously published ultra-high-pressure liquid chromatography–tandem mass spectrometry methodology was used to analyze all stability

study samples for lansoprazole concentration.¹¹ This method was developed and validated according to Food and Drug Administration guidelines for bioanalytical methods.^{12,13} During each day of the study, fresh calibration standards using USP reference standards were prepared in 50:50 v/v water-methanol mixture. The calibration curve consisted of 5 points: 5, 10, 15, 20, and 25 mg/L lansoprazole. Each calibration and validation solution contained 10 mg/L omeprazole. The calibration curves used in the study displayed a linear response in the aforementioned range with a slope of 0.08596 ± 0.00709 , a y -intercept of 0.3525 ± 0.0429 , and an R^2 value of 0.9931 ± 0.0284 . Quantification was performed using the peak area ratios between lansoprazole and omeprazole.

Stability Study

Lansoprazole suspension (3 mg/mL) was prepared in triplicate for both refrigerated (3°C–4°C) and room temperature (20°C–22°C) storage. The suspensions were made by emptying the contents of ten 30-mg generic capsules of lansoprazole into an Erlenmeyer flask and adding 100 mL of 8.4% sodium bicarbonate solution. The suspensions were then stirred on a magnetic stir plate for 30 minutes and protected from light. Following this, the density of each bulk preparation at room temperature was determined using 10-mL samples in a 10-mL graduate cylinder. This 10-mL sample of each was retained for baseline pH determination. Thereafter, 0.6-mL aliquots of suspension were drawn up into plastic amber-colored oral syringes to be stored under the 2 test conditions. Syringes were removed for each time point, the contents were diluted with 8.4 mL of a 50:50 mix of methanol and water, and they were vortex mixed. From this mixture, 100 μ L was removed by micropipette and further diluted with 800 μ L of the 50:50 solvent mixture. A volume of 100 μ L of the internal standard (100 mg/L omeprazole) was added to the aforementioned mixture for a final concentration of 10 mg/L omeprazole. The final dilution of lansoprazole was intended to bring the sample concentration within the calibration range (5–25 mg/L). The actual concentration of lansoprazole in each sample was calculated using the calibration curve from that day. Suspension samples were filtered via a 0.22- μ m filter prior to being added to the autosampler vials.

For each sampling time point, the filled and empty syringes were weighed so as to correct for

Table. Stability of Lansoprazole up to 90 Days at Room Temperature (20°C -22°C) and Refrigerated Temperature (3°C-4°C) Expressed as Mean Concentration (mg/mL) \pm SD and Percent Remaining From Initial Concentration (Time 0 Hours), n=12, for Each Condition at Each Time Point, Determined by LC-MS/MS Using Omeprazole as an Internal Standard*

| Storage | Time Since Compounding | | | | | | | |
|-----------|-------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | 0 hr | 2 hr | 4 hr | 6 hr | 8 hr | 12 hr | 24 hr | 48 hr |
| 20°C-22°C | 2.70 \pm 0.23, 100 | 2.60 \pm 0.14, 96.0 | 2.59 \pm 0.21, 95.9 | 2.55 \pm 0.39, 94.4 | 2.45 \pm 0.25, 90.7 | 2.49 \pm 0.24, 92.2 | 2.47 \pm 0.28, 91.2 | 2.45 \pm 0.28, 90.8 |
| 3°C-4°C | 2.82 \pm 0.16, 100 | 2.78 \pm 0.30, 98.6 | 2.78 \pm 0.12, 99.1 | 2.74 \pm 0.40, 97.1 | 2.71 \pm 0.11, 96.1 | 2.68 \pm 0.16, 95.0 | 2.67 \pm 0.14, 94.6 | 2.65 \pm 0.14, 94.0 |

*Values given are displayed as: mean lansoprazole concentration (mg/mL) \pm SD, percent deviation from initial concentration (concentration at time 0 hours)

density differences between the replicate preparations. This strategy of using the weight of the suspension sample instead of the volume alone has been previously demonstrated as an effective way to compensate for the error involved in sampling a non-homogeneous matrix.¹⁴ At each time point, 2 samples were taken from each replicate, and each sample was injected twice for a total of 4 injections at each time point. Additional samples were analyzed from the bulk suspensions at time 0 hours and at 7, 14, and 30 days to assess the impact of storage in the oral syringes. Finally, the pH of the preparations was monitored at 0 hours and at 7, 14, 21, and 30 days.

Data Analysis

The stability of lansoprazole in the oral suspension preparations was assessed by comparing the percentage of drug remaining at each time point to the initial concentration. Statistical analyses were performed using GraphPad Prism software (GraphPad Software, La Jolla, CA). Additionally, 1-way analysis of variance (ANOVA; $p < 0.05$) with a Dunnett posttest was used to verify statistically significant degradation. The degradation constant (k) was determined from linear regression data of each replicate, assuming first-order kinetics, because the first-order degradation model fit the data better than zero or second order. Using the degradation constants from each temperature condition, the frequency factor and activation energy of degradation were calculated using the Arrhenius equation.⁸ Additional analyses included verification that the replicates within each temperature condition were not statistically different using a repeated-measures ANOVA ($p < 0.05$) and a Bonferroni posttest. The pH measurements between the 2 conditions were also compared using a 2-tailed

Student t -test ($p < 0.05$). Finally, to evaluate the impact of storing the samples in oral syringes versus the bulk suspension, these data were compared using a 1-way ANOVA with Bonferroni multiple comparison test ($p < 0.05$).

RESULTS

Room Temperature Samples Versus Refrigerated Samples

The Table shows the degradation profiles of the lansoprazole suspensions at refrigerated and room temperature conditions. Under refrigeration, the drug concentration in the suspension first dipped below 90% at the 8-day time point, and at 72 hours for room temperature samples. This indicates a beyond-use date of 7 days (refrigerated) and 48 hours (room temperature) for SLS prepared with generic lansoprazole. Statistically significant degradation was verified using the 1-way ANOVA analysis ($p < 0.05$; 0-hour concentration as control). Additionally, within each experimental group the replicates were not shown to have any statistically significant differences. Statistically significant pairing was noted in both groups, with $R^2 = 0.9293$ in the refrigerated group and $R^2 = 0.8794$ among the room temperature replicates.

Degradation Kinetics

Various concentration-versus-time plots were examined for the combination of replicates from each condition, and it was determined that first-order kinetics was the best fit. Using the degradation rate constant (k) for each replicate at each condition, the frequency factor (A) and the activation energy (E_a) were determined from the Arrhenius equation, resulting in $A = 17,354 \text{ hr}^{-1}$ and $E_a = 26.5 \text{ kJ/mol}$. The mean rate constants

Table. Stability of Lansoprazole up to 90 Days at Room Temperature (20°C–22°C) and Refrigerated Temperature (3°C–4°C) Expressed as Mean Concentration (mg/mL) \pm SD and Percent Remaining From Initial Concentration (Time 0 Hours), $n=12$, for Each Condition at Each Time Point, Determined by LC-MS/MS Using Omeprazole as an Internal Standard* (cont.)

| Storage | Time Since Compounding | | | | | | |
|-----------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | 72 hr | 96 hr | 7 days | 8 days | 14 days | 21 days | 30 days |
| 20°C–22°C | 2.37 \pm 0.17, 87.7 | 2.38 \pm 0.21, 87.9 | 2.34 \pm 0.25, 86.7 | 2.34 \pm 0.30, 86.6 | 2.37 \pm 0.07, 87.8 | 2.27 \pm 0.17, 84.1 | 2.27 \pm 0.25, 83.8 |
| 3°C–4°C | 2.63 \pm 0.29, 93.1 | 2.62 \pm 0.16, 92.7 | 2.55 \pm 0.25, 90.5 | 2.50 \pm 0.18, 88.5 | 2.53 \pm 0.26, 89.8 | 2.46 \pm 0.18, 87.2 | 2.43 \pm 0.17, 86.0 |

*Values given are displayed as: mean lansoprazole concentration (mg/mL) \pm SD, percent deviation from initial concentration (concentration at time 0 hours)

for the refrigerated replicate were 0.000187 and 0.000179 hr⁻¹ for the samples stored under room temperature.

Stability of pH

Sample pH was periodically monitored throughout the study. Refrigerated samples held a pH of 8.579 \pm 0.118 (average \pm SD; $n=15$), whereas the room temperature sample pH was 8.578 \pm 0.127 ($n=15$). No statistically significant difference in these data was detected using a 2-tailed Student *t*-test ($p<0.05$) with an R^2 of 3.294e-005, and the relative SD of these measurements was less than 1.5% for each group. This indicates that pH was not a factor in the drug degradation and that the 8.4% sodium bicarbonate was sufficient to maintain pH past the beyond-use time for both temperature conditions.

Impact of Density Correction

Using a density correction to compensate for sampling from a non-homogeneous mixture has been shown to be effective in previous studies on omeprazole stability.¹⁴ The error that is compensated for by this density correction ranges from 0.82% to 17.3%, with a 6.95% mean deviation between the data that were corrected for the weight/density of the sample versus that which were not. The replicates that were refrigerated had a density of 1.073 \pm 0.054 (mean \pm SD; $n=3$), and the room temperature ones had a density of 1.033 \pm 0.0052 ($n=3$). Furthermore, the densities of these 2 groups of preparations were compared using an unpaired, 2-tailed *t*-test, and the means were not found to be statistically different ($p<0.05$).

Impact of Storage in Syringes Versus Bulk Bottles

Finally, the results from the suspension samples stored in amber syringes were compared

with a limited number of sampling points from the bulk (amber-colored) plastic bottles of each replicate. The calculated concentration of lansoprazole at 168-, 336-, and 720-hour time points was compared between the bulk bottles and corresponding oral syringes for each replicate; however, no statistically significant difference was detected ($p<0.05$).

DISCUSSION

Use of Liquid Chromatography–Tandem Mass Spectrometry Technology to Study Drug Stability

Most published drug stability studies use high-performance liquid chromatography with ultraviolet detection for quantification of the drug of interest. In this study, we employed a more sensitive and specific methodology, liquid chromatography–tandem mass spectrometry (LC-MS/MS), because of the concerns regarding rapid degradation of lansoprazole. Unlike ultraviolet detection, mass spectrometric detection correlates to the specific molecular weight of a compound, and with our instrument this molecular weight is accurate out to 0.0001 mass units. This specificity ensures that the chromatographic peak being monitored is in fact that of the drug of interest—in this case lansoprazole—and not a degradation product. Specificity is ensured by monitoring an ion channel specific to the molecular weight of lansoprazole (m/z 370).

Density Correction in Data Analysis

The impact of our correcting for the mass of each of the samples in this study cannot be overstated. When samples from this non-homogeneous suspension are removed by volume, even with a wide-opening pipette tip, their individual contents can vary greatly. Rather than relying on pipette volume to calculate lansopra-

zole concentration in the samples, we used the sample weight and determined the true volume withdrawn using density of each replicate. The precedent for this practice has been set,¹⁴ and we found it to be an effective way to compensate for sampling from non-homogeneous mixtures. This also removes the need for timed shaking for resuspension prior to sampling.

Initial Lansoprazole Concentration

The recipe used for compounding SLS reports an initial concentration of 3 mg/mL, which is expected following complete release of drug from polymer microspheres and 100% dissolution if 300 mg of drug were dissolved in 100 mL of vehicle. However, previous studies have indicated limitations in the dissolution of lansoprazole in sodium bicarbonate, suggesting that Ora-Blend may be a more suitable vehicle for this preparation.⁵ Because of this, we determined an initial, time-0 hours, concentration of each replicate to serve as the reference against which the beyond-use date was calculated. This practice is common in stability investigations because this starting concentration will vary slightly among individual preparations.^{15–18} Nevertheless, our preparations recovered a mean of 90.3% (room temperature replicates) and 94.2% (refrigerated replicates) relative to the theoretical concentration of 3 mg/mL.

Directions for Future Stability Investigations

Work by Ensom et al¹⁹ indicates the stability of lansoprazole in oral suspension can be retained up to 90 days if stored in glass containers. In this study, they also address the important issue of not only a stable preparation, but also a palatable one, showing that the traditional SLS is highly undesirable for oral administration, restricting its use to NG administration.¹⁹ Future investigation is called for that looks at the interactions this drug has with plastic matrices, with regard to storage in plastic prescription bottles, in oral syringes, and administration through NG tubes. Additionally, the practice of reserving all stability study samples at -80°C so they can be analyzed on the same day has the potential to reduce error associated with intraday variations.¹⁹

CONCLUSION

The results of this study indicate that lansoprazole suspension (3 mg/mL) loses stability,

as defined by $>10\%$ reduction of the initial concentration, at 48 hours under room temperature conditions and after 7 days under refrigerated conditions. These study samples were stored in amber-colored oral syringes to protect the drug from light as well as to ensure ease of sampling during the study. The results of this study indicate that the stability of lansoprazole suspension under refrigeration is shorter than previously recognized, if stored in plastic oral syringes. However, this study shows that the 8.4% sodium bicarbonate vehicle is sufficient to maintain the pH of this drug preparation past the beyond-use time, and that storage in amber-colored oral syringes results in stability comparable to that of storage in bulk amber-colored plastic bottles, regardless of temperature. Suspension palatability was not assessed. Finally, the use of density correction to account for differences among non-homogeneous preparations such as SLS allows for more accurate quantification of the drug in small sample volumes.

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ABBREVIATIONS ANOVA, analysis of variance; LC-MS/MS, liquid chromatography–tandem mass spectrometry; NG, nasogastric; PPIs, proton pump inhibitors; SLS, simplified lansoprazole suspension

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